VOLUME 32 · NUMBER 7 · MARCH 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Telehealth Personalized Cancer Risk Communication to Motivate Colonoscopy in Relatives of Patients With Colorectal Cancer: The Family CARE Randomized Controlled Trial

Anita Y. Kinney, Watcharaporn Boonyasiriwat, Scott T. Walters, Lisa M. Pappas, Antoinette M. Stroup, Marc D. Schwartz, Sandra L. Edwards, Amy Rogers, Wendy K. Kohlmann, Kenneth M. Boucher, Sally W. Vernon, Rebecca G. Simmons, Jan T. Lowery, Kristina Flores, Charles L. Wiggins, Deirdre A. Hill, Randall W. Burt, Marc S. Williams, and John C. Higginbotham

Anita Y. Kinney, Antoinette M. Stroup, Sandra L. Edwards, Kenneth M. Boucher, and Randall W. Burt, School of Medicine, University of Utah; Anita Y. Kinney, Lisa M. Pappas, Antoinette M. Stroup, Sandra L. Edwards, Amy Rogers, Wendy K. Kohlmann, Kenneth M. Boucher, Rebecca G. Simmons, and Randall W. Burt, Huntsman Cancer Institute, University of Utah; Marc S. Williams, Intermountain Healthcare, Salt Lake City, UT; Watcharaporn Boonyasiriwat, Chulalongkom University, Bangkok, Thailand; Scott T. Walters, School of Public Health, University of North Texas Health Science Center at Fort Worth, Fort Worth; Sally W. Vernon, The University of Texas School of Public Health, Houston, TX; Marc D. Schwartz, Georgetown University; Marc D. Schwartz, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; Jan T. Lowery, Colorado School of Public Health, University of Colorado, Denver, CO; Kristina Flores, University of New Mexico Cancer Center; Anita Y. Kinney, Charles L. Wiggins, and Deirdre A. Hill, University of New Mexico Cancer Center and School of Medicine, Albuquerque, NM; Marc S. Williams, Genomic Medicine Institute, Geisinger Health System, Danville, PA; John C. Higginbotham, Community and Rural Medicine Institute for Rural Health Research, College of Community Health Sciences, University of Alabama, Tuscaloosa, AL.

Published online ahead of print at www.jco.org on January 21, 2014.

Support information appears at the end of this article.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT01274143.

Corresponding author: Anita Y. Kinney, PhD, RN, Department of Internal Medicine, Division of Epidemiology, Biostatistics and Preventive Medicine, University of New Mexico Cancer Center, 1 University of New Mexico MSC07 4025, Albuquerque, NM 87108; e-mail: AYKinney@salud.unm.edu.

0732-183X/14/3207w-654w/$20.00

DOI: 10.1200/JCO.2013.51.6765

ABSTRACT

Purpose
The rate of adherence to regular colonoscopy screening in individuals at increased familial risk of colorectal cancer (CRC) is suboptimal, especially among rural and other geographically underserved populations. Remote interventions may overcome geographic and system-level barriers. We compared the efficacy of a telehealth-based personalized risk assessment and communication intervention with a mailed educational brochure for improving colonoscopy screening among at-risk relatives of patients with CRC.

Methods
Eligible individuals age 30 to 74 years who were not up-to-date with risk-appropriate screening and were not candidates for genetic testing were recruited after contacting patients with CRC or their next of kin in five states. Enrollees were randomly assigned as family units to either an active, personalized intervention that incorporated evidence-based risk communication and behavior change techniques, or a mailed educational brochure. The primary outcome was medically verified colonoscopy within 9 months of the intervention.

Results
Of the 481 eligible and randomly assigned at-risk relatives, 79.8% completed the outcome assessments within 9 months; 35.4% of those in the personalized intervention group and 15.7% of those in the comparison group obtained a colonoscopy. In an intent-to-treat analysis, the telehealth group was almost three times as likely to get screened as the low-intensity comparison group (odds ratio, 2.83; 95% CI, 1.87 to 4.28; $P < .001$). Persons residing in rural areas and those with lower incomes benefitted at the same level as did urban residents.

Conclusion
Remote personalized interventions that consider family history and incorporate evidence-based risk communication and behavior change strategies may promote risk-appropriate screening in close relatives of patients with CRC.

J Clin Oncol 32:654-662. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Family history of colorectal cancer (CRC) is one of the strongest risk factors for the disease. Inheritance is estimated to play a role in 25% to 30% of patients with CRC.[1,2] Close relatives of patients with CRC have a two- to eight-fold increased risk of the disease when compared with the general population, depending on the age of relatives' diagnoses.[3,4] CRC screening can reduce mortality as a result of the disease by detecting and removing precancerous adenomas and by detecting cancers at an early, often curable stage.[5,6] Several organizations recommend that individuals with intermediate familial risk undergo enhanced screening with colonoscopy no less than every 5 years, beginning either at age 40 years, or 10 years before the age of diagnosis of the youngest family member diagnosed with CRC.[6-8] Unfortunately, the rate of adherence to regular colonoscopic screening in this risk group is far below recommended levels,[9,10] especially among rural and other geographically underserved populations.[11] Contributing factors to suboptimal screening include inadequate familial risk assessment and risk

stratification, poor risk communication (including lack of provider recommendation in primary care settings),[12] inadequate access, and psychosocial factors.[13,14] Limited evidence indicates that written cancer prevention recommendations that are based solely on an individual's family history do not improve risk-appropriate screening.[10] This suggests that risk assessments for nonadherent individuals should be combined with more active interventions, such as engagement of clinicians and strategies that address nonfamilial factors such as psychosocial factors and barriers to screening.

Although the few interventions that have targeted first-degree relatives of patients with CRC demonstrated small to moderate increases in screening, previous studies have not evaluated an intervention's impact on medically verified colonoscopy.[15-17] Furthermore, previous interventions have not assessed intervention impact on rural versus urban dwellers. This is critical, given that remote interventions such as those tested here could help address well-documented barriers in this underserved population.[18] Family history is the most widely available genomic tool,[19] yet it is often underused in clinical practice, behavior change counseling, and risk-appropriate screening recommendations.[20]

METHODS

Study Design

We conducted a cluster randomized, two-group efficacy trial. The key hypothesis guiding this trial was that an intensive, personalized remote intervention (Tele–Cancer Risk Assessment and Evaluation [TeleCARE]) would lead to significant improvements in colonoscopy use 9 months after intervention, compared with a low-intensity targeted mailed intervention. We also hypothesized that the intervention effect would be strongest for urban dwellers, those with higher household incomes, and those who had health insurance.

The trial was approved by the Institutional Review Boards of participating institutions, and all participants provided informed consent. Random assignment began in September 2009 and ended 2 years later. Primary outcome assessments were completed on September 5, 2012.

Study Participants

The majority of the participants (97.1%) were recruited through patients with CRC from five state cancer registries in California, Colorado, Idaho, New Mexico, and Utah. A small number of patients (2.9%) were drawn from Cancer Genetics Network's population-based registries in Colorado, New Mexico, and Utah,[21] and also from two hospital-based registries covering approximately 85% of cancer care in Utah (Intermountain Healthcare and Huntsman Cancer Institute).

Eligibility criteria included the following: age 30 to 74 years; considered at intermediate elevated CRC risk, for whom screening guidelines recommend colonoscopy[6-8] (having a single first-degree relative diagnosed with CRC before age 60 years, or one first-degree biologic relative diagnosed at age 60 years or older plus an additional first- or second-degree biologic relative diagnosed at any age); no colonoscopy in the last 5 years; awareness of family history of CRC; and ability to read and speak English fluently.

Individuals were excluded if they were a member of a family with a molecular or clinical diagnosis of a hereditary cancer syndrome[22]; were currently participating in another research study; received previous clinical or research-based cancer risk counseling; had previously participated in a clinical trial or a behavioral or epidemiologic family cancer study; were mentally incompetent; or had a history of any type of in situ or invasive cancer other than nonmelanoma skin cancer. We did not enroll individuals under age 30 years to limit the possibility of erroneously enrolling members of families with high penetrance hereditary conditions such as familial adenomatous polyposis or Lynch syndrome.

Screening and Random Assignment

Recruitment to the study involved a multistep process, beginning with identification and contact of patients with CRC diagnosed between 1971 and 2009 or their next of kin, and then contact of their relatives, in accordance with each registry's institutional policies. Further details on the study recruitment procedures are described elsewhere.[23] Following the completion of baseline surveys, participants were randomly assigned to one of the study arms using a computer-generated allocation algorithm on the basis of a randomized blocks method (four to eight blocks). Unbeknownst to each family, to avoid experimental contamination, all family members who were enrolled were assigned to the same arm as the first relative to be randomly assigned. Staff who conducted the baseline assessments were not aware of the identity of participating relatives, so as to ensure that they could not predict group assignment of other family members.

Data Collection, Measures, and Primary Outcome Assessment

Eligibility data were collected by telephone. Evidence-based procedures were used for collection of baseline and follow-up data, such as multiple mailings, several survey modes (telephone, mail, web), and $2 incentives to engage nonresponders.[24] Data collectors were blinded to group assignment for the primary outcome assessments.

Each participant self-reported demographic, psychosocial, and clinical data at baseline and 1 and 9 months after intervention. Rural/urban residence determination was based on Rural-Urban Commuting Area codes.[25] The primary outcome was colonoscopy use, as verified by medical records, within 9 months after the intervention. The rationale for the 9-month outcome was based on our and others' previous research that suggested that the intervention effect was most likely to be observed within 6 months.[15,16,26] This time period was extended to 9 months to allow an additional 3 months for individuals living in remote areas where colonoscopy capacity is low and waiting periods are relatively long. Participants who reported colonoscopy were asked to provide written consent to obtain their colonoscopy reports.

Study Interventions

Figure 1 briefly describes the interventions and depicts how the TeleCARE arm was more intensive than the control arm. The interventions are briefly described below and are described in more detail elsewhere.[27]

Educational Brochure

Participants in the comparison group received a mailed, study-specific educational brochure that was targeted to their familial risk status.

TeleCARE

Participants in the TeleCARE group received a theoretically based[28,29] intervention consisting of several components. Immediately after completion of the baseline survey, participants were mailed the same educational brochure as the comparison group participants and tailored visual aids in a sealed envelope with instructions to not open until the telephone session with one of five cancer risk specialists (ie, genetic counselors). The sessions were conducted within 1 month after completion of the baseline survey and tailored based on the participant's responses to key items assessed at baseline: family history of CRC; psychosocial factors such as perceptions about CRC risk and severity; beliefs about colonoscopy; and personal factors such as CRC screening history and knowledge, health care access, social support, and barriers to screening. TeleCARE incorporated risk communication and behavior change approaches designed to raise participant perceptions about the threat of familial CRC, arouse fear, enhance beliefs about colonoscopy benefits, and increase self-efficacy and motivation to undergo the procedure. Participants were informed that colonoscopy was the recommended screening strategy because of their risk status. TeleCARE was delivered using the client style of motivational interviewing, which is a client-centered and directive approach for enhancing intrinsic motivation.[29] All sessions were audio-taped to assess treatment fidelity. Sessions lasted an average of 39 minutes (standard deviation, 12.2). A tailored letter, summarizing key aspects of the TeleCARE session, was mailed immediately after the telephone session and outlined the participants' stated initial steps toward obtaining a colonoscopy. With the participants' consent, a

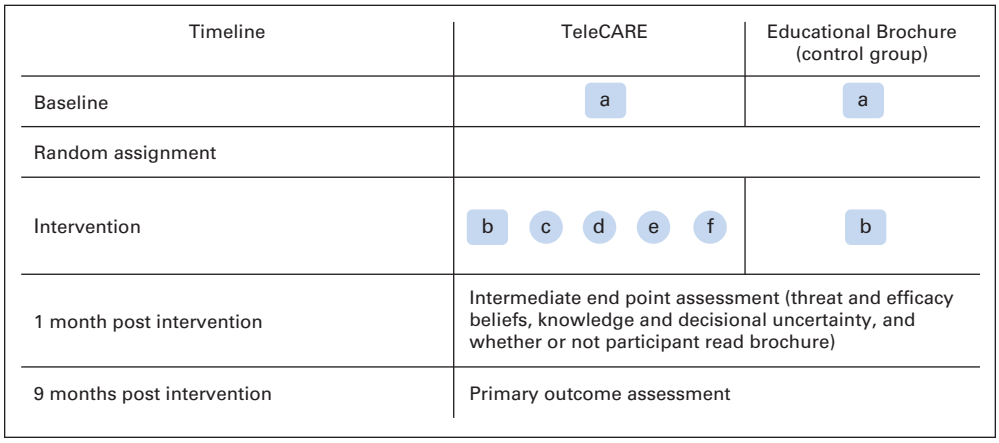

Fig 1. Graphical depiction of the high- and low-intensity interventions. (a) Survey to determine self-reported baseline clinical information, including colonoscopy screening, family history of cancer, sociodemographics, and psychosocial data; (b) mailed educational brochure targeted to participants' risk status; (c) mailed tailored visual aids; (d) tailored telephone cancer risk assessment and counseling session; (e) mailed tailored summary letter of TeleCARE (Tele–Cancer Risk Assessment and Evaluation) session; (f) mailed tailored reminder card.

copy of this and their family cancer history (pedigree) was mailed to the participants' health care provider to encourage further discussion.

The five TeleCARE interventionists were certified genetic counselors employed by the Huntsman Cancer Institute. All were experienced in conducting familial cancer risk assessment and risk counseling. They received initial training in the theoretical foundations of the intervention, the clinical protocol, and motivational interviewing, and they piloted TeleCARE with four analog patients each, with audiotaped sample sessions, before implementing the intervention with participants. Throughout the study, interventionists met regularly with a clinical supervisor to monitor the fidelity of the intervention.

Because health care provider communication about colonoscopy is an important predictor of cancer screening behavior,[30] with the participant's consent, copies of the participant's personalized letter and family cancer history in the form of a pedigree were mailed to the participant's provider to encourage further discussion.

Statistical Analysis

The planned and final outcome analyses included eligible and randomly assigned relatives of patients with CRC. Between-group differences in demographic and clinical variables were tested with *t* tests and χ^2 tests. The intervention effect on colonoscopy use was determined with generalized mixed logistic regression models to account for the familial effect. We tested the effect of the interventions for those with a known outcome. Additionally, an intent-to-treat analysis included all eligible participants who were randomly assigned, regardless of whether they withdrew or completed any of the follow-up surveys. Both negative and multiple imputation methods were used to estimate colonoscopy uptake in those with an unknown outcome. We determined whether the intervention effect estimates were sensitive to imputation. Negative outcome imputation assumed that if there was no documented verification of colonoscopy, the procedure did not occur. Multiple imputation was based on verified colonoscopy within 9 months and demographic information, including age, sex, marital status, education level, employment status, household income, health insurance coverage, Rural-Urban Commuting Area code status, and number of first- and second-degree relatives with CRC. Multiple imputation estimates also combined inference from five imputed data sets.[31] Variables assessed in the a priori exploratory intervention effect modification analysis included rural status, health insurance status, and household income. Variables in the multiple imputation algorithms were adjusted to exclude possible effect modifiers. The odds of colonoscopy uptake were estimated within potential modifier subgroups and compared with the overall odds ratio and 95% CI. Analyses were conducted by two biostatistician coauthors (K.M.B. and L.M.P.), who were blinded to the intervention assignments using SAS (version 9.3; SAS Institute, Cary, NC).

The direct costs associated with the interventions were estimated on the basis of study staff and interventionist salaries, and all labor, telephone, mail, and printing costs associated with delivery of the interventions. The costs of implementing the intervention for each additional colonoscopy received in the TeleCARE group were estimated by first summing the costs associated with intervention delivery, then calculating the number of additional colonoscopies received in the TeleCARE group relative to the comparison group, and lastly, dividing the total costs of the intervention by the number of additional colonoscopies received.[32]

We calculated that a sample size of 219 participants per group would provide at least 80% power to detect a between-group difference of 12% in the use of colonoscopy within 9 months. An initial unadjusted sample size per group (s0 = 142) was calculated using NQuery Advisor 7.0 (Statistical Solutions, Cork, Ireland),[33] taking only the hypothesized difference in colonoscopy rates (8% *v* 12%) into account, and assuming the use of a two-group Fisher's exact binomial test for equality of binomial proportions. Alpha was set at .05, the test was two-sided, and 80% power was required. Adjustment for intraclass correlation was made using the variance inflation adjustment for group-randomized studies: s1 = (1 + [mean cluster size −1] × intraclass correlation)s0.[34] A mean family cluster size of 1.4 and intraclass correlation coefficient of 0.12 was assumed. The sample size was further inflated to account for estimated retention (on the basis of our previous experiences) and success at obtaining records by dividing s1 by the product of the hypothesized retention rate (80%) and the hypothesized success rate of obtaining colonoscopy reports (85%) to obtain the final sample size of 219 per group.

RESULTS

Study Cohort

The study enrollment, random assignment, and retention data are shown in Figure 2.[35] Of those deemed to be eligible after initial assessment (n = 614), 496 participants (80.7%) were randomly assigned to one of the two study arms; 15 individuals were found to be ineligible after random assignment. Eligible individuals who underwent randomization (n = 481) were included in the analysis; 94% in the TeleCARE arm received their allocated intervention. Only 3% reported that they did not read the mailed materials; thus, we are not able to tease out the effect of each intervention component. With regard to sex, race, ethnicity, number of first-degree relatives with CRC, and year of relatives' diagnosis, randomly assigned participants

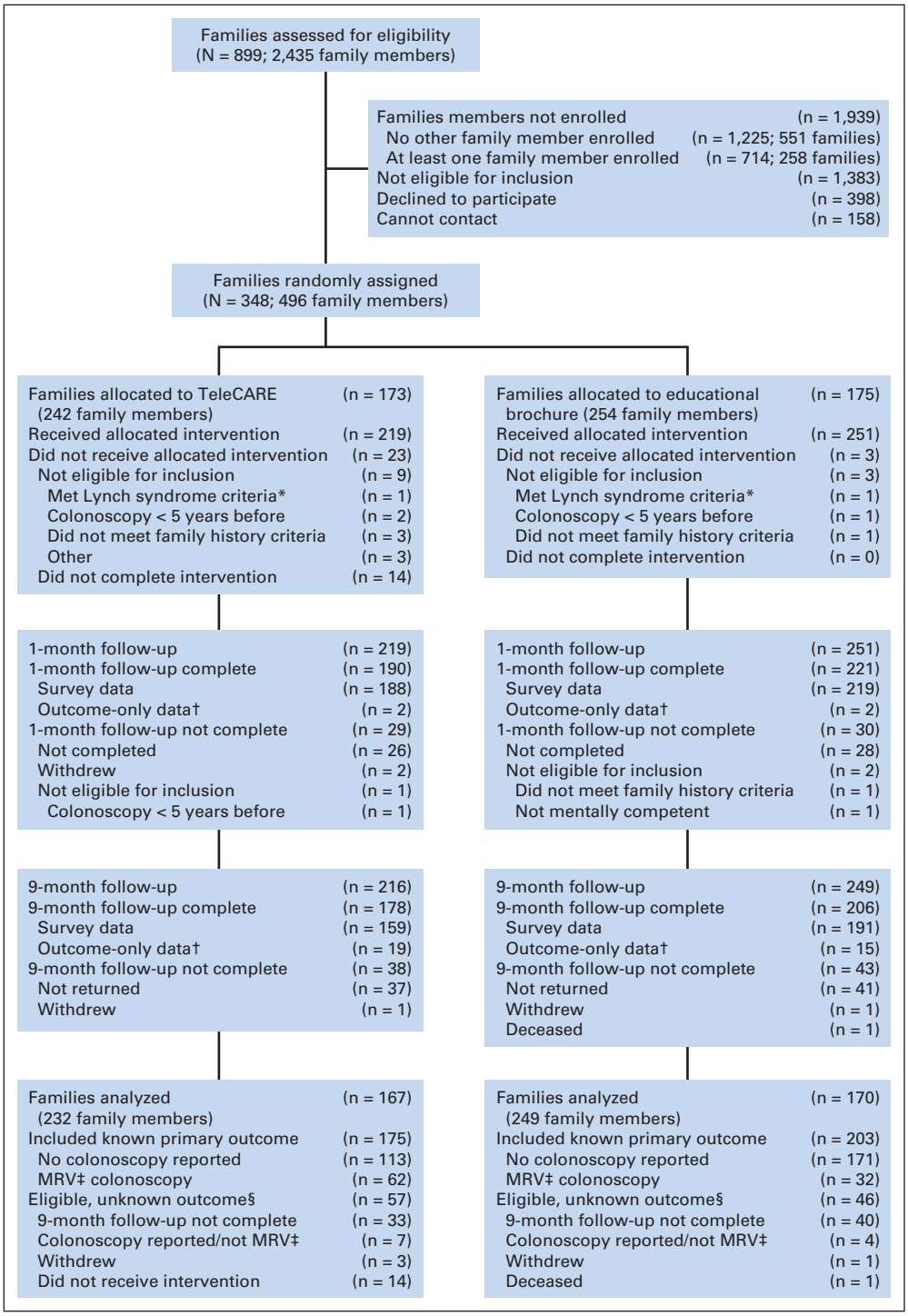

Fig 2. Diagram showing screening, random assignment, and follow-up of the study participants. (*) Based on work by Tan et al.[35] (†) Participants who did not complete a survey were asked to complete a very brief survey containing primary outcome questions only. (‡) Medical-record verified (MRV). (§) Included in imputation analysis. TeleCARE, Tele–Cancer Risk Assessment and Evaluation.

were not significantly different from those who were deemed eligible at screening but who did not enroll.[23] Fifty-two percent had another family member enrolled onto the study. Individuals were more likely to enroll when other family members also participated ($P = .02$) and self-reported a previous colonoscopy ($P = .03$). The retention rate was 79.8%, with no significant difference in the percentage of participants from each arm who were available at 9 months for assessment of colonoscopy uptake. Participants whose 9-month outcome data on key demographic and clinical factors were unknown did not differ from those whose outcome data were known.

Participants in the two groups did not differ with respect to baseline demographic or clinical characteristics (Tables 1 and 2). A total of 81.7% of patients had health insurance, and 22.7% resided in a rural area. The family cluster size was 1.4. Thirty-eight percent of participants' primary care providers were mailed copies of these materials.

Table 1. Baseline Characteristics by Intervention Group for Intent-to-Treat Analysis

Characteristic	Overall (n = 481)		TeleCARE (n = 232)		Comparison Group (n = 249)	
	No.	%	No.	%	No.	%
Age, years						
Mean	50.3		49.9		50.8	
SD	9.0		9.0		9.0	
Sex						
Female	276	57.4	91	39.2	114	45.8
Male	205	42.6	141	60.8	135	54.2
Race/ethnicity						
Non-Latino white	454	94.4	215	92.2	239	96.0
Latino	17	3.5	9	3.9	8	3.2
Other/unreported	10	2.1	8	3.5	2	0.8
Marital status						
Single	21	4.4	10	4.3	11	4.4
Married	363	75.5	172	74.1	191	76.7
Separated, widowed, divorced	97	20.2	50	21.6	47	18.9
Educational level						
High school or less	93	19.3	51	22.0	42	16.9
Post high school	206	42.8	100	43.1	106	42.6
Bachelor's degree	114	23.7	50	21.6	64	25.7
Postgraduate	68	14.1	31	13.4	37	14.9
Rural/urban residence*						
Urban	372	77.3	173	74.6	199	79.9
Rural	109	22.7	59	25.4	50	20.1
Household income (annual)						
< $15,000	39	8.1	24	10.3	15	6.0
$15,000-29,999	49	10.2	22	9.5	27	10.8
$30,000-49,999	91	18.9	42	18.1	49	19.7
$50,000-69,999	73	15.2	38	16.4	35	14.1
≥ 70,000	180	37.4	81	34.9	99	39.8
Missing/refused to respond	49	10.2	25	10.8	24	9.6
Employment status						
Employed	338	70.3	166	71.6	172	(69.1)
Unemployed	143	19.7	66	28.5	77	30.9
Health insurance						
Private	339	70.5	164	70.7	175	70.3
Public	54	11.2	31	13.4	23	9.2
No coverage	87	18.1	37	16.0	50	20.1
Refused to respond	1	0.2	0	0.0	1	0.4
Has a personal health care provider						
Yes	313	65.1	152	65.5	161	64.7
No	143	29.7	68	29.3	75	30.1
Missing	25	5.2	12	5.2	13	5.2

Abbreviations: ERS, Economic Research Service; RUCA, rural-urban computing area; SD, standard deviation; TeleCARE, Tele–Cancer Risk Assessment and Evaluation; USDA, US Department of Agriculture; WWAMI, Washington, Wyoming, Alaska, Montana, and Idaho.

*Rural/urban residence was based on RUCA codes at the zip code level. RUCA codes were developed by the University of Washington Rural Health Research Center and the USDA ERS, with the support of the federal Health Resource and Service Administration's Office of Rural Health Policy and the ERS using standard Census Bureau urbanized area and urban cluster definitions in combination with work commuting data to characterize census tracts and later zip codes. The 10 RUCA categories were aggregated into urban (1-3) and rural (4-10), as recommended by the WWAMI Rural Health Research Center.

Primary Outcome

A significantly higher proportion of individuals in the TeleCARE group received a colonoscopy by the 9-month follow-up compared with those in the low-intensity group (34.5% *v* 15.7%; $P < .001$). The intervention effect was observed in per-protocol and intent-to-treat models, regardless of imputation method (Table 3).

Subgroup Analysis

Neither the analysis that included only those with evaluable outcome nor the intent-to-treat analysis showed evidence of effect modification that was associated with rural status or household income (Fig 3). No individuals in the brochure-only group without insurance had a medically verified colonoscopy at 9 months; therefore, an accurate intervention effect within the subgroup with no insurance could not be estimated. The intraclass correlation coefficient[36] associated with the random variation resulting from familial clustering was low (0.015). The addition of this random component did not statistically improve the fit of the models based on likelihood ratio tests.

Table 2. Family Cluster Characteristics by Intervention

Characteristic	Overall		TeleCARE		Comparison	
	No.	%	No.	%	No.	%
No. of families	337	100.0	167	49.6	170	50.4
No. enrolled from the family						
1	230	68.2	119	71.4	111	65.3
2	79	23.5	38	28.8	41	24.1
3-5	28	8.3	10	5.8	18	10.6
No. of FDRs and SDRs with CRC	481		232		249	
1 FDR, 0 SDRs	390	81.1	188	81.0	202	81.1
≥ 2 FDRs, 0 SDRs	31	6.4	13	5.6	18	7.2
1 FDR, 1 SDR	52	10.8	30	12.9	22	8.8
1 FDR, ≥ 2 SDRs	6	1.3	0	0.0	6	2.4
≥ 2 FDRs, 1 SDR	2	0.4	1	0.4	1	0.4

Abbreviations: CRC, colorectal cancer; FDR, first-degree relative; SDR, second-degree relative; TeleCARE, Tele–Cancer Risk Assessment and Evaluation.

The direct cost of delivering TeleCARE was estimated to be $42.20 per participant; for the print-only intervention, the cost was $8.20. The difference in colonoscopy rates between the two groups was 19.7%, resulting in 34 additional colonoscopies in the TeleCARE group (Table 3). The estimated total cost of the TeleCARE intervention was calculated at $9,790 for the 232 participants in this group. Thus, each additional colonoscopy in the TeleCARE group was estimated to cost $287.95.

DISCUSSION

This two-group efficacy trial used a population-based approach to recruit and enroll members of families at intermediate risk for CRC and to evaluate two remote risk communication interventions involving either personalized telephone counseling and tailored print materials (TeleCARE) or a mailed educational brochure. We found a nearly three-fold increase in colonoscopy uptake among individuals who received the TeleCARE intervention compared with those who received the targeted print materials. Evidence from nonrandomized studies indicates that the benefits of colonoscopy include reductions in incidence and mortality in first-degree relatives of patients with CRC.[37-39] Results from these epidemiologic studies underscore the potential impact of our intervention.

Our observed effect size was higher than that reported in a personalized risk communication trial of siblings of patients with CRC, in which self-reported colonoscopy was considered in the primary outcome analysis.[15] In the sibling study, the addition of telephone counseling to the tailored mailed print materials did not have an incremental effect. Findings from studies in average-risk individuals have also documented that more intensive interventions are not always better.[15,40-43]

The impact of the intervention was similar for urban and rural dwellers and was not affected by income category. This is encouraging because our study was motivated, in part, to address geographic barriers to cancer risk assessment and counseling, as well as suboptimal screening rates. These findings suggest that TeleCARE was robust even among those in geographically underserved areas and with lower incomes. Only three of the 65 individuals without health insurance obtained a colonoscopy, indicating that lack of health insurance is a major barrier to accessing colonoscopy and that behavioral interventions do not appreciably overcome this barrier. Provisions in the Affordable Care Act,[44] if effectively implemented, could potentially increase access to colonoscopy for the uninsured or underinsured.

The direct cost of TeleCARE per additional colonoscopy was $287.95. To our knowledge, there are no cost analyses of behavioral interventions in target populations similar to ours for comparison.

Table 3. Generalized Mixed Model Results for Intervention Effect on Colonoscopy Uptake Within 9 Months

Model*	Odds of Having Colonoscopy, TeleCARE *v* Comparison	95% CI	*P*	Medically Verified Colonoscopies			
				TeleCARE		Comparison	
				No.	%	No.	%
Outcome known	2.93	1.79 to 4.81	< .001	62 of 175	35.4	32 of 203	15.7
Intent-to-treat							
Negative outcome imputation†	2.47	1.53 to 3.98	< .001	62 of 232	26.7	32 of 249	12.9
Multiple imputation‡	2.83	1.87 to 4.28	< .001	80 of 232	34.5	43 of 249	17.3

Abbreviations: MI, multiple imputation; TeleCARE, Tele–Cancer Risk Assessment and Evaluation.
*Each of the three separate models (outcome known, negative outcome imputation, and multiple imputation) represents a different treatment of missing outcomes and included a random effect for family.
†Negative outcome imputation treated unknown colonoscopy outcome as no colonoscopy.
‡Average number of colonoscopies based on five imputation sets from the SAS (SAS Institute, Cary, NC) procedure MI.

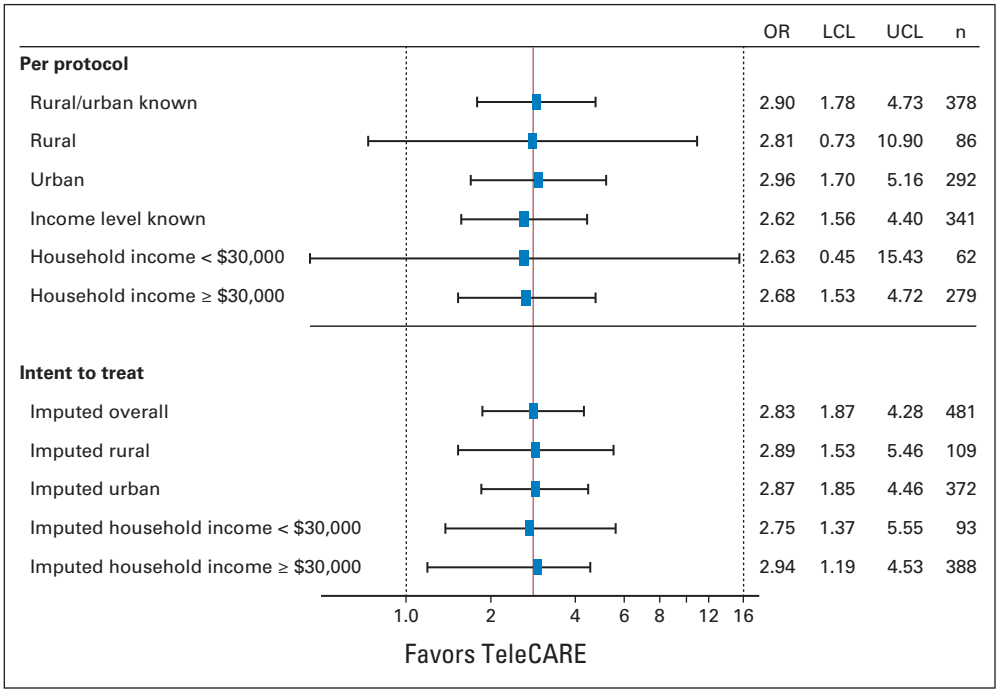

Fig 3. Investigation of effect modification of subgroups on the odds of colonoscopy uptake and 95% CI. TeleCARE, Tele–Cancer Risk Assessment and Evaluation.

Although colonoscopy screening every 5 years in family members of patients with colorectal cancer has value, the cost-benefit and cost-effectiveness of such an approach is not clear.[45] Future behavioral intervention work should conduct a planned comprehensive analysis.

The study had several limitations. Eligible individuals who did not enroll onto the study, or those for whom outcome data were not available, may have differed systematically across the groups in attributes that we could not observe. Another limitation is the small number of participants from underserved racial and ethnic groups. The subgroup analyses were exploratory and not sufficiently powered to draw definitive conclusions. Our finding that family enrollment affected study participation[23] suggests that it may have influenced the trial's outcome. We were not able to assess this directly, but we encourage future work to assess family communication patterns of enrollees. Ethical constraints precluded the inclusion of a no-intervention control group; however, it seems that a number of participants responded favorably to the low-intensity intervention.

An important limitation is that we were not able to disentangle the contributions of the multiple components of TeleCARE in achieving the desired outcome. However, future plans include process,[46] mediation, and moderation analyses to evaluate possible mechanisms of action and subgroups for whom TeleCARE was more or less effective. In future studies, a more intensive telephone-based cancer risk assessment and counseling session could be reserved for those who do not respond to either generic or personalized printed materials after a period of time. A stepped-care approach[47] that is integrated into community oncology practices or health systems that routinely collect family history data, and that systematically increases the intervention intensity, may be a cost-effective alternative approach in this risk group. Cancer registries might adopt such an approach to ensure broad reach of interventions that target relatives of patients with CRC. One-on-one telephone counseling with a cancer risk counselor in a centralized location may be reserved for those who do not respond to the other intervention components. Future work is also needed to evaluate whether use of other kinds of practitioners (eg, health educators) yields equivalent results. Future stepped-care or comparative effectiveness trials could inform value-driven clinical practice and public health policies with regard to implementing the types of interventions studied here.

The study's strengths include a population-based recruitment approach, a randomized design, inclusion of an appreciable number of rural dwellers, verification of colonoscopy, and provision of the clinical intervention remotely so as to enhance access.

Our findings suggest that a multifaceted remote cancer risk assessment and telephone counseling intervention that incorporates personalized print materials is more effective than an intervention that makes use of nontailored educational print materials alone. We also found that TeleCARE had an impact on rural dwellers that was similar to that observed in urban dwellers. These results provide evidence to guide clinical practice and future research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Randall W. Burt, Myriad Genetics (C) **Stock Ownership:** None **Honoraria:** Randall W. Burt, Myriad Genetics **Research Funding:** None

Expert Testimony: None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Anita Y. Kinney, Lisa M. Pappas, Antoinette M. Stroup, Marc D. Schwartz, Wendy K. Kohlmann, Kenneth M. Boucher, Sally W. Vernon, Rebecca G. Simmons, Randall W. Burt, John C. Higginbotham
Administrative support: Amy Rogers
Provision of study materials or patients: Antoinette M. Stroup, Wendy K. Kohlmann, Jan T. Lowery, Kristina Flores, Charles L. Wiggins, Deirdre A. Hill, Marc S. Williams
Collection and assembly of data: Anita Y. Kinney, Lisa M. Pappas, Sandra L. Edwards, Amy Rogers, Jan T. Lowery, Kristina Flores, Deirdre A. Hill, Marc S. Williams
Data analysis and interpretation: Anita Y. Kinney, Lisa M. Pappas, Marc D. Schwartz, Kenneth M. Boucher, Jan T. Lowery, Charles L. Wiggins
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Lichtenstein P, Holm NV, Verkasalo PK, et al: Environmental and heritable factors in the causation of cancer: Analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343:78-85, 2000

2. Kerber RA, Neklason DW, Samowitz WS, et al: Frequency of familial colon cancer and hereditary nonpolyposis colorectal cancer (Lynch syndrome) in a large population database. Fam Cancer 4:239-244, 2005

3. Butterworth AS, Higgins JP, Pharoah P: Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis. Eur J Cancer 42:216-227, 2006

4. Johns LE, Houlston RS: A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 96:2992-3003, 2001

5. Zauber AG, Winawer SJ, O'Brien MJ, et al: Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 366:687-696, 2012

6. Levin B, Lieberman DA, McFarland B, et al: Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 134:1570-1595, 2008

7. Burt RW, Barthel JS, Dunn KB, et al: NCCN clinical practice guidelines in oncology: Colorectal cancer screening. J Natl Compr Canc Netw 8:8-61, 2010

8. American Cancer Society: American Cancer Society Recommendations for Colorectal Cancer Early Detection. Atlanta, GA, American Cancer Society, 2011. http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-acs-recommendations

9. Courtney RJ, Paul CL, Carey ML, et al: A population-based cross-sectional study of colorectal cancer screening practices of first-degree relatives of colorectal cancer patients. BMC Cancer 13:13, 2013

10. Rubinstein WS, Acheson LS, O'Neill SM, et al: Clinical utility of family history for cancer screening and referral in primary care: A report from the Family Healthware Impact Trial. Genet Med 13:956-965, 2011

11. Anderson AE, Henry KA, Samadder NJ, et al: Rural vs urban residence affects risk-appropriate colorectal cancer screening. Clin Gastroenterol Hepatol 11:526-533, 2013

12. Greiner KA, Engelman KK, Hall MA, et al: Barriers to colorectal cancer screening in rural primary care. Prev Med 38:269-275, 2004

13. Kinney AY, Hicken B, Simonsen SE, et al: Colorectal cancer surveillance behaviors among members of typical and attenuated FAP families. Am J Gastroenterol 102:153-162, 2007

14. Jacobs LA: Health beliefs of first-degree relatives of individuals with colorectal cancer and participation in health maintenance visits: A population-based survey. Cancer Nurs 25:251-265, 2002

15. Manne SL, Coups EJ, Markowitz A, et al: A randomized trial of generic versus tailored interventions to increase colorectal cancer screening among intermediate risk siblings. Ann Behav Med 37:207-217, 2009

16. Rawl SM, Champion VL, Scott LL, et al: A randomized trial of two print interventions to increase colon cancer screening among first-degree relatives. Patient Educ Couns 71:215-227, 2008

17. Glanz K, Steffen AD, Taglialatela LA: Effects of colon cancer risk counseling for first-degree relatives. Cancer Epidemiol Biomarkers Prev 16:1485-1491, 2007

18. MacDowell M, Glasser M, Fitts M, et al: A national view of rural health workforce issues in the USA. Rural Remote Health 10:1531, 2010

19. Valdez R, Yoon PW, Qureshi N, et al: Family history in public health practice: A genomic tool for disease prevention and health promotion. Annu Rev Public Health 31:69-87, 2010

20. Flynn BS, Wood ME, Ashikaga T, et al: Primary care physicians' use of family history for cancer risk assessment. BMC Fam Pract 11:45, 2010

21. Anton-Culver H, Ziogas A, Bowen D, et al: The Cancer Genetics Network: Recruitment results and pilot studies. Community Genet 6:171-177, 2003

22. Heald B, Church J, Plesec T, et al: Detecting and managing hereditary colorectal cancer syndromes in your practice. Cleve Clin J Med 79:787-796, 2012

23. Simmons R, Lee Y, Stroup A, et al: Examining the challenges of family recruitment to behavioral intervention trials: Factors associated with participation and enrollment in a multi-state colonoscopy intervention trial. Trials 14:116, 2013

24. Dillman D, Smyth J, Christian L: Internet, Mail, and Mixed-Mode Surveys: The Tailored Design Method (ed 3). Hoboken, NJ, John Wiley & Sons, 2009

25. University of Washington Rural Health Research Center: Rural-urban commuting area codes (version 2.0), 2006. http://depts.washington.edu/uwruca/

26. Lowery JT, Marcus A, Kinney A, et al: The Family Health Promotion Project (FHPP): Design and baseline data from a randomized trial to increase colonoscopy screening in high risk families. Contemp Clin Trials 33:426-435, 2012

27. Pengchit W, Walters ST, Simmons RG, et al: Motivation-based intervention to promote colonoscopy screening: An integration of a fear management model and motivational interviewing. J Health Psychol 16:1187-1197, 2011

28. Witte K: Putting the fear back into fear appeals: The extended parallel process model. Commun Monogr 59:329-349, 1992

29. Moyers TB, Martin T, Manuel JK, et al: Assessing competence in the use of motivational interviewing. J Subst Abuse Treat 28:19-26, 2005

30. Beydoun HA, Beydoun MA: Predictors of colorectal cancer screening behaviors among average-risk older adults in the United States. Cancer Causes Control 19:339-359, 2008

31. Rubin DB: Multiple imputation for nonresponse in surveys. New York, J. Wiley & Sons, 1987, pp 166-167

32. Paskett E, Tatum C, Rushing J, et al: Randomized trial of an intervention to improve mammography utilization among a triracial rural population of women. J Natl Cancer Inst 98:1226-1237, 2006

33. Elashoff JD: NQuery Advisor Version 7.0 User's Guide. Cork, Ireland, Statistical Solutions, 2007

34. Donner A, Klar N: Design and Analysis of Cluster Randomization Trials in Health Research. London, United Kingdom, Arnold, 2000, p 178

35. Tan YY, McGaughran J, Ferguson K, et al: Improving identification of Lynch syndrome patients: A comparison of research data with clinical records. Int J Cancer 132:2876-2883, 2013

36. Snijders TAB, Bosker R: Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling (ed 2). London, United Kingdom, SAGE Publications, 2011, p 368

37. Dove-Edwin I, Sasieni P, Adams J, et al: Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 331:1047, 2005

38. Dowling DJ, St John DJ, Macrae FA, et al: Yield from colonoscopic screening in people with a strong family history of common colorectal cancer. J Gastroenterol Hepatol 15:939-944, 2000

39. Järvinen HJ, Mecklin JP, Sistonen P: Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 108:1405-1411, 1995

40. Myers RE, Bittner-Fagan H, Daskalakis C, et al: A randomized controlled trial of a tailored navigation and a standard intervention in colorectal cancer screening. Cancer Epidemiol Biomarkers Prev 22:109-117, 2013

41. Costanza ME, Luckmann R, Stoddard AM, et al: Using tailored telephone counseling to accelerate the adoption of colorectal cancer screening. Cancer Detect Prev 31:191-198, 2007

42. Marcus AC, Mason M, Wolfe P, et al: The efficacy of tailored print materials in promoting colorectal cancer screening: Results from a randomized trial involving callers to the National Cancer Institute's Cancer Information Service. J Health Commun 10:83-104, 2005 (suppl 1)

43. Vernon SW, Bartholomew LK, McQueen A, et al: A randomized controlled trial of a tailored

interactive computer-delivered intervention to promote colorectal cancer screening: Sometimes more is just the same. Ann Behav Med 41:284-299, 2011

44. Patient Protection and Affordable Care Act, 2010. http://www.gpo.gov/fdsys/pkg/BILLS-111hr3590enr/pdf/BILLS-111hr3590enr.pdf

45. Ramsey SD, Wilschut J, Boer R, et al: A decision-analytic evaluation of the cost-effectiveness of family history-based colorectal cancer screening programs. Am J Gastroenterol 105:1861-1869, 2010

46. Craig P, Dieppe P, Macintyre S, et al: Developing and evaluating complex interventions: The new Medical Research Council guidance. BMJ 337: a1655, 2008

47. Green BB, Wang CY, Anderson ML, et al: An automated intervention with stepped increases in support to increase uptake of colorectal cancer screening: A randomized trial. Ann Intern Med 158:301-311, 2013

Support

Supported by the National Cancer Institute (Grant No. 1R01CA125194-0305; A.Y.K.) and a grant from the Huntsman Cancer Foundation. The study was also supported by the Shared Resources (Grant No. P30 CA042014) at Huntsman Cancer Institute (Biostatistics and Research Design, Genetic Counseling, Research Informatics, the Tissue Resource and Applications Core, and the Utah Population Database); the Utah Cancer Registry (funded by Contract No. HHSN261201000026C from the National Cancer Institute's SEER program with additional support from the Utah State Department of Health and the University of Utah); the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885, the National Cancer Institute's SEER Program under Contract No. N01PC-2010-00034C awarded to the Northern California Cancer Center, Contract No. N01-PC-35139 awarded to the University of Southern California, and Contract No. N01-PC-54404 awarded to the Public Health Institute, and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under Contract No. U58CCU000807-05 awarded to the Public Health Institute; the Colorado Central Cancer Registry program in the Colorado Department of Public Health and Environment funded by the National Program of Cancer Registries of the Centers for Disease Control and Prevention; the Cancer Data Registry of Idaho supported in part by the National Program of Cancer Registries of the Centers for Disease Control and Prevention; the New Mexico Tumor Registry (funded by National Cancer Institute Contract No. HHSN261201000033C); the Rocky Mountain Cancer Genetics Network (Contract No. HHSN261200744000C); the Huntsman Cancer Registry; and the Intermountain Healthcare Oncology Clinical Program and Intermountain Clinical Genetics Institute.

This content is solely the responsibility of the authors and does not necessarily reflect the opinions or views of the funding and supporting agencies.

Acknowledgment

We thank the Family CARE Project participants and their affected relatives, who made this research possible; Clearwater Research for providing assistance with the conduct of the trial; Al Marcus, PhD, for his input on the study design; Susan Schulman, MAT, for her assistance with manuscript preparation; and Roger Edwards, BS, programmer/analyst. We also thank the interventionists: Amanda Gammon, MS; Kory W. Jasperson, MS; Wendy K. Kohlmann, MS; Anne Naumer, MS; and Lisa M. Wadge, MS, who are genetic counselors in High Risk Clinical Research at Huntsman Cancer Institute, and Anita Pascoe for contact with Intermountain patients.